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(54) PHARMACEUTICAL COMPOSITIONS AND PHARMACEUTICAL CAPSULE SHELLS

(71) We, ROHM G.M.B.H., a German Body Corporate of Darmstadt, Germany, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to a process for preparing coated pharmaceutical compositions and pharmaceutical capsule shells.

Medicinal formulations such as tablets or coated tablets are often provided with coatings which are either insoluble in water or only soluble at particular pH values. Such coatings are generally applied from solutions in an organic solvent. For example, Belgium Patent No. 717,236 described the production of such coatings using aqueous dispersions of the coating material which has the advantage that it is necessary to use relatively expensive organic solvents which cannot in practice generally be recovered; moreover, the danger of fire and explosion resulting from solvent vapours is avoided.

However, the process according to the Belgian patent has the disadvantage that only water-insoluble coating films can be produced. The spontaneous release of the active ingredient by dissolution of the coating in the stomach or in a particular portion of the intestine is not possible with such coatings. Thus, the active ingredient can only be released if water or alkali-soluble substances are incorporated in coatings of polyvinyl chloride, polyvinyl acetate or polyacrylates, which substances can be dissolved out in the gastro-intestinal tract leaving voids through which the active ingredient can diffuse out. However, a sufficiently rapid and complete decomposition of such medicinal formulations often requires the use of special additives in the core, i.e. so-called disintegrating agents. Moreover, it is often extremely difficult in the production of such medicinal formulations on an industrial scale to set the decomposition time of the coating to a constant value.

By the use of solutions of coating materials in organic solvents, it has been possible to prepare coated medicinal products wherein one can pre-determine the time and location in the digestive tract at which the coating will decompose or the active ingredient diffuse through the coating. These pre-determined values can be varied over a wide range. However, this has not generally been possible to the same extent using dispersions of coating agents.

According to German Auslegeschrift No. 1,219,175 veterinary preparations may be coated with a coating, which is insoluble in the stomach, of a copolymer of dialkylaminoalkylamides of acrylic or methacrylic acid with suitable comonomers e.g. the lower esters of said acids. The copolymers can be applied in the form of a solution or a dispersion. Such copolymers have advantages over conventional tablet coating lacquer solutions, the binder of which is composed of dialkylaminoalkyl esters and alkyl esters of acrylic or methacrylic acid, the disadvantage according to said Auslegeschrift of the latter solutions being the susceptibility to saponification of dialkylaminoalkyl esters of acrylic or methacrylic acid.

Coating agents containing an emulsion copolymer of dimethylaminoethyl - methylacrylamide and methyl methylacrylate produced according to German Auslegeschrift No. 1,219,175 often however provide very hard and brittle coatings which splinter off when subjected to mechanical stress e.g. in packing machines. It has been found that this disadvantage could not be entirely obviated by the use of ethyl or butyl acrylate in place of methyl methacrylate although the brittleness slightly decreased as a result of this measure.

We have now found that improved coatings can be obtained by the use of aqueous dispersions of polymers containing 10 to 55% of units from vinyl monomers containing carboxy groups and/or monoalkyl- or dialkyl-aminoalkyl ester groups.

According to one feature of the present invention we provide pharmaceutical compositions for oral administration which comprise discrete units of therapeutic material provided with at least one protective coating or shell produced from an aqueous dispersion (is hereinafter defined) of a polymer containing 10 to 55% by weight of units from at least one olefinically unsaturated monomer containing one or more carboxy groups and/or one or more monoalkyl- or dialkyl aminoalkyl or β-morpholino- or β-piperidino-ethyl carboxylate ester groups.

According to a further feature of the present invention, we provide a process for the preparation of pharmaceutical compositions for oral administration which comprises applying to discrete units of therapeutic material at least one coating of an aqueous dispersion (as hereinafter defined) of a polymer containing 10 to 55% by weight of units from at least one olefinically unsaturated monomer containing one or more carboxy groups and/or one or more monoalkyl- or dialkylaminoalkyl or β-morpholino- or β-piperidino-ethyl carboxylate ester groups with subsequent drying to form a protective coating.

The term "dispersion" is used herein to denote a system comprising a continuous aqueous phase in which are suspended solid (polymer) particles having a particle size of 0.02 to 1 μm, as measured for example in conventional manner, e.g. according to the method of H. Lange, Kolloid-Zeitschrift und Zeitschrift für Polymere, (1968), Vol. 223 (1), 24 by determination of the turbidity and refractive index of the dispersion. When viewed under an electron microscope the particles have a generally spherical appearance. These dispersions have a milky appearance and 1 mm thick films of the dispersion are opaque or only slightly translucent. As used herein the term "dispersion" does not extend to solutions or colloidal systems of polymers which, in contrast to the above dispertions, are generally clear or have a cloudy appearance. 1 mm thick films of such solutions or colloidal systems are either clear or have a slightly cloudy appearance.

We have found that tough elastic coatings for pharmaceutical compositions which do not tend to splinter can be produced by carrying out the above-described process according to the invention. Those coatings which are prepared from polymers containing dialkylaminoalkyl carboxylate ester groups, e.g. dimethylaminoethyl methacrylate, have been found to be soluble in gastric juice, while those coatings which are prepared from polymers containing carboxy groups have been found to be soluble only in the alkaline medium of the intestine. The sensitivity to saponification which was found to be a disadvantage with tablet coatings produced from solutions of dialkylaminoalkylester group-containing polymers has not been observed with the coatings produced from dispersions according to the process of the present invention.

The above-described process according to the invention may be carried out for example by applying to the discrete units of therapeutic material at least one coating of a coating composition comprising the above-defined dispersion, the coated material being subsequently dried.

The coatings prepared according to the present invention are generally water-insoluble in part of the pH range between 1.5 and 8 and soluble or swellable in water in another part of this range. If the coatings are prepared from carboxy group-containing polymers the insolubility range is located at pH values below 7 while the water solubility or swellability range is generally at neutral to weakly alkaline pH values. Amino-ester group-containing polymer coatings are however generally insoluble in the alkaline range and soluble or swellable in the neutral or weakly acid range.

The polymers containing carboxy groups are preferably derived from acrylic or methacrylic acid, the latter being particularly preferred. However other polymerisable mono- or di-carboxylic acids such as crotonic, itaconic, maleic or fumaric acid can also be employed. In view of their two acidic groups, dicarboxylic acids are added in half the molar quantity as compared with monocarboxylic acids.

Polymers containing monoalkyl- or dialkylaminoalkyl or β-morpholino- or β-peridino-ethyl ester groups include those derived, for example, from cyclo hexaylamineethyl acrylate or methacrylate, dimethylaminoethyl acrylate or methacrylate, diethylaminoethyl acrylate or methacrylate, dibutylaminoethyl acrylate or methacrylate, β-morpholinoethyl acrylate or methacrylate, β-piperidinoethyl acrylate or methacrylate, 2 - (dimethylamino) - propyl acrylate or methacrylate, 2 - (diethylamino) - butyl acrylate or methacrylate, 4 - (dimethylamino) - butyl acrylate or methacrylate. Corresponding esters of other α, β-unsaturated acids such as maleic or itaconic acid can also be used, but these are less important from the industrial point of view compared with said acrylic and methacrylic acid esters.

In addition to the above-described monomers with carboxy or amino ester groups, other vinyl monomers without such groups comprise 45 to 90% by weight of the polymers. The characteristics of the coating film can be considerably influenced by suitable selection of latter monomers.

The co-monomers can generally be classified according to whether they impart to the resulting polymer more or less hardness or

more or less hydrophilic properties. Monomers which lead to an increase in hardness include lower esters of methacrylic acid, particularly methyl methacrylate, as well as acrylo- and methacrylonitrile, styrene, α-methyl-styrene, vinyltoluene, vinylchloride and vinyl acetate. Elasticity and extensibility are in particular provided by the use of acrylic acid esters as co-monomers.

It is note-worthy that the dependence of the film softness or extensibility on the size of the alkyl ester group does not follow the general rule observed with corresponding solution polymers where softness and extensibility of the film increase with increasing size of the ester alkyl group. Consequently the films produced from the polymer dispersions employed in accordance with the present invention are not only harder than films obtained from a solution of an identical polymer but with increasing size of the alkyl ester group there is an increase in the film hardness. The maximum degree of elasticity is obtained with ethyl acrylate as the co-monomer, together with e.g. methacrylic acid, whilst n-butyl acrylate provides considerably more brittle films. Monomers which may be used to provide polymer coating having good extensibilty include various olefins such as ethylene, butadiene, chlorobutadiene and isoprene.

Monomers giving polymers having strongly hydrophilic properties and which are non-salt containing or salt forming, the hydrophilic properties of which are consequently substantially independent of the pH value, include acrylamide and methacrylamide, hydroxyethyl acrylate and methacrylate, β-hydroxypropyl acrylate and methacrylate, β-hydroxyl-butyl acrylate and methacrylate, α-hydroxybutyl acrylate and methacrylate, glycerin monoacrylate and methacrylate. A similar effect is observed with polymers containing vinyl alcohol units. A particularly pronounced hydrophilising action, independent of pH value, is possessed by polymerisable quaternary ammonium salts such as e.g. methacryloxy - ethyl - trimethyl - ammonium chloride.

If a hydrophobising action is desired then monomers with aromatic or higher aliphatic groups are advantageously employed. Examples of such monomers include n-butyl, n-hexyl, n-octyl, 2-ethylhexyl, cyclohexyl, benzyl and dodecyl esters of unsaturated polymerisable carboxylic acids, particularly acrylic and methacrylic acid as well as the higher N-alkyl-amides of such acids, vinyl esters of higher fatty acids such as butyric acid, valeric acid or versatic acids and vinyl-aromatics, such as styrene or vinyltoluene.

The wide possible variation in the composition of the polymer which may be employed in the process according to the invention enables one to prepare pharmaceutical compositions to meet practically any requirement. Compositions which should not release their active ingredient in the acid medium of the stomach are provided with a coating having a dialkylaminoalkyl ester group-containing polymer. The time or rate of release of the active ingredient can be determined in general by the content of said amino ester groups in the polymer. If the content is close to the above-mentioned upper limit then the medicinal formulation dissolves within a few minutes and thereupon releases the active ingredient. An increase in the amino ester content above the indicated limit of 55% by weight provides no further advantages, but may lead to the danger that the coatings become sticky in humid air. By lowering the amino ester proportion, the decomposition time of the composition can be delayed, as it is by the use of hydrophobic comonomers; however the quantity the latter co-monomers should not be so high that the residence time of the composition in the acid medium of the stomach is not sufficient for its dissolution. In some cases, amino ester group-containing polymers are already readily water-soluble in the neutral range. This can lead to difficulties in production of the compositions and to the desired dissolution of the coating in the saliva when the composition is administered. In this case, it is advantageous to adjust the proportion of amino ester group-containing monomers in the polymer to values close to the indicated lower limit, and if necessary to improve the water-solubility in the acid range by incorporating hydrophilic monomers, particularly hydroxyalkyl esters of acrylic and/or methacrylic acid.

If it is not intended to dissolve the composition coating but to liberate the active ingredient by diffusion, then either a weakly cross-linked polymer can be used e.g. obtained by polymerising a monomer composition containing small amounts of a bifunctional vinyl compound such as divinyl benzene or glycol dimethylacrylate, or part of the aminoester can be replaced by other, optionally hydrophilic, but not acid-soluble monomers.

Amino esters generally give relatively soft films. To provide adequate hardness and resistance to high atmospheric humidity and/or reasonably elevated temperatures as may occur during tablet coating or storage of the compositions in a pocket close to the body or in a glove compartment of a car, hardness-improving comonomers may be incorporated into the said polymer. This effect may be obtained, for example, with monomers having an extensive hardening action such as styrene, methyl methacrylate or acrylonitrile with quite small additions e.g. 10 to 30% by weight of the monomer mixture, whereas with monomers having a less

pronounced hardening action e.g. butyl methacrylate or vinyl acetate, larger quantities are desirably employed. The hardness of the polymer should not h wever be increased to such an extent that brittle coatings which crack off during mechanical stressing are obtained.

In many cases it is desirable that the coated composition does not decompose or become diffusion-permeable in the stomach but in the neutral or weakly alkaline medium of the intestine. Coatings having such properties may be obtained according to the invention by the use of emulsion polymers composed of 10 to 55% by weight of carboxy group-containing monomers.

Coatings having a high content of carboxy groups dissolve particularly easily in neutral to weakly alkaline medium of the upper intestine if they also contain hydrophilic units. As the carboxy group content decreases, the speed of dissolution falls, but this effect is compensated in part by the fact that the undissolved composition has a longer residence time in the intestine with a higher pH value and a correspondingly increasing dissolving capacity. Coatings with a carboxy group content at the lower limit of the above-specified range and which optionally contain also a proportion of hydrophobic monomer units are generally no longer dissolved in the parts of the intestine with the highest pH value, but only become permeable to diffusion as a result of swelling.

Duffusion tablets the coating of which remains undissolved during the passage through the intestine and which only permits the diffusion of the enclosed active ingredient, can be produced according to the invention by the use of cross-linking monomers with at least two polymerisable double bonds in the preparation of said polymers, examples of such cross-linking monomers being indicated above. Coatings with two separate solubility ranges in the acid and alkaline zones respectively and insolubility in the neutral zone can be produced from dispersions of those polymers containing carboxy and amino ester groups respectively.

Acrylic or methacrylic acid units impart hardness to the polymer. To ensure an adequate film elasticity, hardening monomers should only be used if the polymerisable carboxylic acid forms a relatively low polymer proportion. When high proportions of acrylic or methacrylic acid are used, advantageously only softening monomers particularly ethyl acrylate are used as co-monomers. Dispersions based on methacrylic acid are generally much more stable than those based on acrylic acid and are therefore preferred particularly with a high acid content.

The dispersions employed in the process according to the invention may be prepared in conventional manner. The solids content of the dispersion is advantageously in the range of 20 to 50%. The said dispersion will generally contain an emulsifier, the nature of which will depend on the capacity of the monomers or polymers to f rm salts. Thus carboxy group-containing monomers are preferably polymerised in the presence of anionic emulsifiers, and amino ester group-containing monomers preferably in the presence of cationic emulsifiers. Non-ionic emulsifiers such as e.g. ethoxylated fatty alcohols, fatty acid amides or alkyl phenols with approximately 20 to 100 mol of ethylene oxide per mol of hydrophobic compound, are generally suitable for both types of monomer group and can be used in combination with anionic emulsifiers for the polymerisation of amino group-containing monomers. Examples of such anionic emulsifiers include soaps or compounds prepared by sulphating and neutralizing the above-indicated ethylene oxide adducts. Monomer mixtures with a high carboxy group content are advantageously used with mixtures of non-ionic and anionic emulsifiers. Preferred cationic emulsifiers for the polymerisation of amino ester group-containing monomer mixtures are e.g. (diisobutylphenoxyethoxy-ethyl) - dimethyl - benzylammonium - chloride or stearyl - dimethyl - benzyl ammonium - chloride. They can optionally be used mixed with non-ionic emulsifiers. The emulsifier quantity based on the aqueous phase is advantageously at least 0.5 and preferably 1 to 5% by weight.

The dispersions employed in the present invention are preferably prepared by the monomer feed process where the monomer mixture is gradually introduced into an aqueous solution of the emulsifier and the initiator. Preferably polymerisation is carried out at 60 to 90°C and potassium or ammonium persulphate or 4,4' - dicyano - 4,4'-azo - valeric acid are preferably used as initiators. The molecular weight of the polymer can be regulated by a corresponding selection of the initiator quantity or by the addition of sulphur regulators such as 2-ethyl-hexyl thioglycolate.

The dispersions obtained may be mixed with additives such as dyes, fillers or pigments and used directly for coating the therapeutic material. To this end a conventional tablet coating vessel may be employed, coating being effected by spraying or pouring the dispersion on to the therapeutic material. To accelerate drying, air particularly hot air, may be blown in to evaporate the water. It is also possible to use the fluidisation process whereby the dispersions are sprayed into the fluid bed and the units of therapeutic material are simultaneously agitated and dried by the air blown in. In the portion feed process, 10 to 30 coatings may be applied which in the case of pure lacquer

layers form a coating having a total thickness of 10 to 50 mμ. When using pigments and other adjuvants, the coating thickness may be from 20 to 200 mμ. Depending on the properties desired, various lacquer coats which may be coloured or uncoloured, gastric juice-resistant or gastric juice-soluble, can be combined. It is also possible to incorporate active ingredients into the lacquer coats. It may also be advantageous to incorporate therapeutic material between two or several coats in order to bring about a gradual release of the material after individual lacquer coats have dissolved. In addition to tablets, coated tablets, capsules, micro-dragees and granulates, active ingredient powders can also be coated with the said dispersions. The requirement for lacquer substances is naturally dependent on the surface and form of the particle because in most cases a closed film coat is sought while such a coat is not always obtained with the same number of coats. The described dispersions can also be used for granulating medicinal powders, either in order to improve their ease of tabletting or the release of active ingredient from the thus obtained tablet. By the use of increased quantities of polymer in the tablet mass and by applying the polymer to the surface of the particles by compressing, so-called matrix tablets may be prepared from which the medicinal substances are released in retarded manner in the digestive tract. By the appropriate use of dispersions of gastric juice-soluble or intestinal juice-soluble polymers of varying permeability, the time and place of liberation of active ingredient in the digestive tract can be controlled.

If water sensitive active ingredients or compositions are to be covered with aqueous polymer dispersions, it is advantageous first to apply a protective film of a corresponding polymer dissolved in organic solvents. However, other protective films which may also be employed include those derived from materials soluble in organic solvents and which are more hydrophobic such as shellac, wax, cellulose ether, cellulose ester, etc., such protective films also being used to coat the tablets prior to the sugar coating process.

In many cases it is necessary or desirable to produce pharmaceutical compositions by enclosing the therapeutic material in powder or granulate form in a prefabricated capsule shells. By the use of the said polymer dispersions, capsule shells can be produced having the same solubility characteristics as coatings of the dispersion applied directly to the therapeutic material. When using known gelatin capsules, a delayed release of active ingredient can only be achieved by an additional coating with a lacquer substance with delayed solubility. Said process is however uneconomic due to the additional process stage. It is also possible to produce capsules with retarded solubility in the digestive juices from corresponding polymers by injection moulding in the thermoplastic state. However, at the high processing temperatures necessary, the properties of these polymers vary uncontrollably and in particular the solubility characteristics change. As opposed to this the use of the said dispersions according to the invention permits the production in simple and reliable manner of medicinal capsule shells of precisely determined solubility characteristics.

Thus, according to a further feature of the present invention we provide a process for the production of pharmaceutical capsule shells which comprises coating the surface of a mould with a composition comprising an aqueous dispersion (as hereinbefore defined) of a polymer containing 10 to 55% by weight of units from at least one olefinically unsaturated monomer containing one or more carboxy groups and/or one or more monoalkyl- or dialkyl - aminoalkyl or β - morpholino- or β-piperidino-ethyl carboxylate ester groups, the coating being subsequently dried and removed from the mould.

This can generally be carried out using a mould in the form of a mandrel having the shape of the capsule shell to be produced which is immersed in the dispersion of the polymer so that it is covered with a coating of the polymer. Drying takes place and the finished capsule shell is removed from the mould core. In order to obtain greater coating thickness the mould core may be immersed several times and dried. If desired the composition of the coating mass can be varied for each immersion process. The drying can also be accelerated in known manner by means of a hot air flow.

To accelerate the conversion of the liquid coat formed by immersion into a solid capsule, the still wet coating can be immersed for example in a coagulant e.g. a strong electrolyte solution.

Although immersion is the simplest and most advantageous method for producing capsule shells, particularly since one can readily vary the length of the capsule according to depth of immersion, other processes for producing capsules from the polymer dispersions can be employed. For example, the mould core may be sprayed with the coating dispersion to produce a coating of the desired thickness. If desired, simultaneous drying can be effected with hot air. It is also possible to use a hollow mould and coat this on the inside by spraying or pouring in a coating of the dispersion. The mould cores on which the capsules are formed should be free from under-cuts and have surface characteristics such that the dried capsules can be easily removed. The removal of the finished capsule can be carried out using for example separa-

ting agents which are applied to the mould core prior to coating.

The polymer dispersions can, if desired, be thickened to enable an adequate coat thickness to be obtained by a single immersion operation. To this end e.g. the acidity of the coating mass can be brought close to the pH value at which the polymer is soluble in water. By swelling the polymer particles, the viscosity of the substrate is increased.

Further additives such as dyes, fillers, sugars, etc., can serve to improve the appearance and for taste of the coating as well as protect against possible confusion. To this end the capsule, particularly when it is already filled and sealed can be coated with sugar or other conventional water soluble table coating lacquers.

The following Examples illustrate the present invention.

Example 1

A. Preparation of the dispersion

In a Witt pot with reflux condenser, stirrer and supply vessel at 80°C, 0.12 g of sodium salt of 4,4 - azobis - (4 - cyano - valeric acid) and 1.2 g of the sodium salt of a sulphated adduct of triisobutylphenol with 7 mol of 50% ethylene oxide (Hostapal BV conc. of Farbwerke Hoechst, the word "Hostapal" is a registered Trade Mark) are dissolved in 240 g of distilled water. An emulsion previously prepared from 160 g of ethyl acrylate, 120 g of methyl methacrylate, 120 g of dimethylaminoethylmethacrylate, 4.8 of the above indicated emulsifier, 1.08 of the above indicated initiator and 365 g of distilled water is added dropwise at 80°C over four hours to the above solution. On completion of the addition the mixture is kept for 2 hours at 80°C and then cooled to room temperature. For the separation of the coagulated material, the dispersion is filtered through a fine mesh sieve of stainless steel.

A coagulate-free low viscous 40% dispersion is obtained which dries to a clear colourless flexible non-adhesive film.

B. Coating the tablets

2 kg of tablets with a diameter of about 7 mm, height 4 mm and weight of 150 mg were heated to 40 to 50°C by blowing hot air into a tablet coating vessel. The above-described dispersion was diluted with water to a 50% solids content and 200 g was poured in 10 g portions onto the rotating tablets. The hot air supply was interrupted in each case for about 15 to 30 seconds until a uniform distribution of the dispersion on the tablets was obtained and then subsequently drying took place for about 2 minutes with hot air. After about 1 hour the total quantity was applied. The tablets were finally dry-blown with hot air accompanied by slow rotation and finally dried by exposing to the air overnight on gratings.

Example 2

A. Preparation of dispersion

Processing was carried out as described in Example 1 but using as the monomer a mixture of 240 g of ethyl acrylate, 100 g of methyl methacrylate and 60 g of dimethylaminoethyl - methacrylate. A low viscous dispersion with a 40% solid material content is obtained.

B. Coating the tablets

45 g of talc, 30 g of titanium dioxide and 7 g of red lacquer ZLT (Siegle) were suspended with water, made up to 200 g and finely dispersed in a ball mill. This pigment suspension was mixed with 50 g of the above-obtained dispersion and the mixture applied in portions of 10 to 15 g within 1 hour to 2 g of tablets rotating in a tablet coating vessel. The coated tablets were subsequently dried over-night in a drying cabinet at 40°C. The coated tablets decomposed in synthetic gastric juice according to DAB VII within 5 minutes.

Example 3

A. Preparation of the dispersion

Processing was carried out as described in Example 1 but using a monomer mixture of 180 g of ethyl acrylate, 100 g of methyl methacrylate and 120 g of cyclohexyl aminoethylmethacrylate is used. The coagulate formed during polymerisation is filtered off and a low viscous dispersion is obtained which dries to a clear colourless robust flexible film; the dispersion has a solids content of about 40%.

B. Coating the tablets

The above dispersion was diluted to a dry solids content of 20% and 150 g thereof was applied in 10 portions of 15 g each to 2 kg of tablets. Accompanied by rotation in the tablet coating vessel and blowing in of hot air the dispersion was distributed within 30 seconds. The drying time before the next portion was introduced was 3 minutes. After 40 minutes the application process was completed. The coated tablets were spread out and dried in air.

Example 4

A. Preparation of the dispersion

Processing was carried out as described in Example 1 using the following monomer composition:

180 g of ethyl acrylate;
120 g of methyl methacrylate;
80 g of dimethylaminoethyl methacrylate;
20 g of ethyleneglycol monomethacrylate.

The monomer emulsion in the supply vessel is stirred during the entire feed period.

A low viscous dispersion is obtained which is dried to a clear colourless flexible non-adhesive film, the solids content of the dispersion is 39%.

B. Coating the tablets

2 kg of tablets with a diameter of approximately 7 mm, a height of 3.8 mm and a weight of 140 mg were initially covered with a 12.5% solution of a copolymer of dimethylaminoethyl methacrylate and methyl methacrylate in acetone, and dried with hot air accompanied by rotation. As described in Example 1 this was followed by the application of 50 g of the above-obtained 40% dispersion in 4 portions within 30 minutes followed by drying with hot air so that the tablets finally had a temperature of 40°C. The tablets were then dried overnight on gratings.

Example 5

A. Preparation of the dispersion

In a Witt pot with a reflux condenser, stirrer and supply vessel at 80°C, 0.7 g of ammonium peroxide disulphate, 10.5 g of the sodium salt of an adduct prepared from triisobutyl phenol and 7 mol ethylene oxide (50%, trade name: Hostapal BV conc. of Farbwerke Hoechst) together with 10.5 g of an adduct prepared from isononylphenol and 9 mol of ethylene oxide were dissolved in 700 g of distilled water. To the solution accompanied by stirring within 4 hours at 80°C were added dropwise a previously prepared monomer mixture of 150 g of ethyl acrylate, 150 g of methacrylic acid and 0.6 g of thioglycolic acid - 2 - ethylhexyl ester. At the end of feed-in the mixture was kept for a further 2 hours at 80°C, cooled to room temperature and filtered through a fine mesh sieve made from stainless steel.

A low viscous 30% dispersion is obtained which dries to a clear hard brittle non-adhesive film.

B. Coating the tablets

a) 490 g of the above-obtained dispersion were mixed with 15 g of triacetin as a softener and poured in portions of 10 to 15 g onto 2 kg of tablets rotating in a tablet coating vessel. For the purpose of drying, hot air was blown in so that the temperature of the tablets gradually rose to 30 to 40°C. The tablets were dried overnight in air and tested for gastric juice resistance. In the decomposition test prescribed in DAB VII no decomposition in synthetic gastric juice was observed in 2 hours. In artificial intestinal juice the tablets dissolved within 30 minutes.

b) 1150 g of the same dispersion was diluted with 1700 g of water, 60 g of talcum were stirred in and the mixture was sprayed in a fluidisation device (Glatt WSLD) on to 5 kg of tablets within 35 minutes at a feed temperature of 60°C. Finally after turning off the air heating, gentle rotation was carried out for a further 10 minutes and the coated tablets were dried overnight on gratings in a drying cabinet at 50°C. The tablets meet the requirements of DAB VII relative to gastric juice-resistant coated tablets.

Example 6

A. Preparation of the dispersion

Processing was carried out as described in Example 5 but in addition 3 g of acrylamide were added to the mixture and the monomer composition was as follows:

147 g of ethyl acrylate;
150 g of methacrylic acid; and
0.6 g of thioglycolic acid - 2 - ethyl ester.

A low viscous 30% dispersion was obtained which dried to a clear slightly turbid brittle film.

B. Coating the tablets

On to 2 kg of tablets in a tablet coating vessel were initially poured 10 ml of a 12.5% solution of a copolymer of equal parts of methacrylic acid and methyl methacrylate in isopropanol, drying being effected by means of hot air. Then a pigment suspension of 40 g of talc, 10 g of titanium dioxide, 30 g of dye pigment orange lacquer ZLT 2 (Siegle), 10 g of bentonite (Veegum F) and 10 g of polyethyleneoxide of molecular weight 6000 in 400 g of water was prepared by dispersing in the ball mill and mixed with 100 g of the above-obtained resin dispersion diluted to a solids content of 25%.

This mixture in the tablet coating vessel was then sprayed on to the previously protected tablets with the aid of a pneumatic pressure spray gun. After a spraying period of about 1 minute the tablets were well moistened and the dye well distributed. Spraying was then interrupted and drying took place for about 2½ minutes by blowing in hot air. Spraying and drying were repeated about 20 times until a smooth coating of uniform colour was obtained. The tablets were gastric juice-resistant according to DAB VII and decomposed in synthetic intestinal juice within 20 minutes.

Example 7

Processing was carried out as described in Example 5 but using a monomer mixture of

75 g of ethyl acrylate;
75 g of butyl acrylate;
150 g of methacrylic acid; and
0.9 g of thioglycolic acid - 2 - ethylhexyl ester.

A low viscous 30% dispersion was obtained.

Example 8

Processing was carried out as described in Example 5 but using a monomer mixture of

150 g of methyl acrylate;
150 g of methacrylic acid; and
0.6 g of thioglycolic acid - 2 - ethylhexyl ester.

Upon completion of the polymerisation an approximately 10% coagulate was filtered off. A low viscous dispersion with a solids content of 29% was obtained.

Example 9

Processing was carried out as described in Example 5, but using a monomer mixture of

90 g of ethyl acrylate;
120 g of 2-ethylhexyl acrylate;
90 g of acrylic acid;
0.6 g of thioglycolic acid-2-ethylhexyl ester.

A low viscous dispersion with a solid content of 30% was obtained, which was processed as quickly as possible after preparation.

Example 10

Processing was carried out as described in Example 5, but in addition 15 g of acrylamide were added to the mixture and the monomer composition was as follows:

195 g of ethyl acrylate;
90 g of acrylic acid.

A medium viscous dispersion was obtained which dried to a clear colourless robust hard film; the dispersion had a solid content of 30%.

Example 11

1.6 g of the sodium salt of 4,4 - azo - bis-(4 - cyano - valeric acid), 12 g of the sodium salt of a sulphated adduct of triisobutylphenol with 7 mol of ethylene oxide, 50% (trade name Hospatal BV conc. of Farbwerke Hoechst) and 12 g of an adduct prepared from isononylphenol and 9 mol of ethylene oxide were dissolved in 871 g of distilled water in a Witt pot with reflux condenser, stirrer and supply vessel at 80°C. To the solution were added dropwise accompanied by stirring within 4 hours at 80°C, a previously prepared monomer mixture of 100 g of ethyl acrylate, 40 g of dimethylaminoethyl methacrylate and 60 g of methacrylic acid. After addition was completed, the mixture was kept for 2 hours at 80°C and then cooled to room temperature. The coagulate formed during polymerisation was filtered off using a fine mesh screen made from stainless steel.

A low viscous dispersion with a solid material content of 16% was obtained which dried to a cohesive thin layer flexible film. Such a 30 μm thick film is soluble in turbid form in artificial stomach juice at pH 1.3 within 30 seconds and soluble in clear form in artificial intestinal juice at pH 6.8 within 20 seconds.

Example 12

A 40% dispersion prepared acc rding to Example 1A from ethyl acrylate ester, methyl methacrylate and dimethylaminoethyl methacrylate is warmed to a temperature of 25°C in an immersion bath with stirrer. P lished glass rods with rounded ends are carefully degreased with acetone and immersed for 3 seconds, dried accompanied by rotation in a weak air flow at 40°C and 20 to 40% relative atmospheric humidity, the process being repeated twice more. The film coating deposited on the immersed body is cut off smoothly at the upper edge, pushed off with a tube adjacent to the immersed body and the appropriate capsule halves are assembled. Transparent medicament capsules are obtained which dissolve in the gastric juices.

Example 13

Rounded polished metal rods made from stainless steel are carefully degreased and initially immersed for 2 seconds in a solution of 16 g of calcium acetate in 200 g of water and 100 g of ethanol. The wetted rods are kept, accompanied by rotation for 60 seconds in an atmosphere of 25°C and 40 to 60% relative atmospheric humidity and then immersed for 5 seconds in a dispersion prepared according to Example 5A of equal parts of ethyl acrylate and methacrylic acid mixed with 20 parts of glycerin triacetate per 100 parts of polymer as the softener. The separated coagulate is dried to a film at 35°C and 20 to 40% relative atmospheric humidity accompanied by rotation and separated into bodies according to Example 12 and assembled to form medicament capsules. In this way transparent to translucent capsules are obtained which do not dissolve in the gastric juices but gradually dissolve and decompose in intestinal juices so that the medicaments contained therein are released within 30 to 60 minutes.

Example 14

50 parts of a dispersion prepared according to Example 5A from ethyl acrylate and methacrylic acid having a 30% solids content are mixed with 100 parts of a finely ground pigment suspension of the following composition:

10 parts of talcum;
5 parts of titanium dioxide;
5 parts of variegated pigment (trade name Lebensmittelgelback ZLT 2, Siegle);
1 part of polyvinylpyrrolidone (trade name Lebensmittelgelblack ZLT 2,
3 parts of polyoxyethylene sorbitan mono-stearate (Tween 80; the word "Tween" is a registered Trade Mark);
76 parts of water;

100 parts.

Accompanied by continuous stirring the bodies described in Example 13, and similarly treated with calcium acetate solution, are immersed in this mixture for 6 seconds and treated further as in Example 13. In this way non-transparent yellow medicament capsules are obtained which do not decompose in the gastric juices within a period of 2 hours, but which slowly dissolve in the intestinal juices.

WHAT WE CLAIM IS:—

1. Pharmaceutical compositions for oral administration which comprise discrete units of therapeutic material provided with at least one protective coating or shell produced from an aqueous dispersion (as hereinbefore defined) of a polymer containing 10 to 55% by weight of units from at least one olefinically unsaturated monomer containing one or more carboxy groups and/or one or more monoalkyl- or dialkyl- aminoalkyl or β-morpholino- or B - piperidino - ethyl carboxylate ester groups.

2. Compositions as claimed in claim 1 wherein the said polymer contains 10 to 55% by weight of units from acrylic and/or methacrylic acid.

3. Compositions as claimed in claim 1 wherein the said polymer contains 10 to 55% by weight of units from crotonic, itaconic, maleic or fumaric acid.

4. Compositions as claimed in claim 1 wherein the said polymer contains 10 to 55% by weight of units from at least one monoalkyl- or dialkyl- aminoalkyl or β - morpholino- or Z - piperidino - ethyl ester of acrylic or methacrylic acid.

5. Compositions as claimed in claim 4 wherein the said polymer contains 10 to 55% by weight of units from at least one monomer selected from cyclohexylaminoethyl acrylate or methacrylate, dimethylaminoethyl acrylate or methacrylate, diethylaminoethyl acrylate or methacrylate, dibutylaminoethyl acrylate or methacrylate, β - morpholinoethyl acrylate or methacrylate, β - piperidoethyl acrylate or methacrylate, 2 - (dimethylamino) - propyl acrylate or methacrylate, 2 - (diethylamino)-butyl acrylate or methacrylate, and 4 - (dimethylamino) - butyl acrylate or methacrylate.

6. Compositions as claimed in any of claims 2, 4 or 5 wherein the said polymer contains a total of 10 to 55% by weight of units from acrylic and/or methacrylic acid and from at least one monoalkyl- or dialkyl- aminoalkyl ester of acrylic or methacrylic acid.

7. Compositions as claimed in any of the preceding claims wherein the said polymer also contains units from at least one alkyl ester of acrylic or methacrylic acid.

8. Compositions as claimed in claim 7 wherein the said ester is ethyl acrylate.

9. Compositions as claimed in claim 7 wherein the said ester is methyl methacrylate.

10. Compositions as claimed in any of the preceding claims wherein the said polymer also contains units from acrylo- or methacrylo-nitrile, styrene, α-methyl-styrene, vinyl-toluene, vinyl chloride and/or vinyl acetate.

11. Compositions as claimed in any of the preceding claims wherein the said polymer also contains units from acrylamide or methacrylamide, and/or at least one hydroxy-alkyl ester of acrylic or methacrylic acid.

12. Compositions as claimed in claim 11 wherein the said hydroxy-alkyl ester comprises hydroxyethyl acrylate or methacrylate, β-hydroxypropyl acrylate or methacrylate, β-hydroxy - butyl acrylate or methacrylate, or glycerin monoacrylate or methacrylate.

13. Compositions as claimed in any of the preceding claims wherein the said polymer also contains units from at least one polymerisable olefinically quaternary ammonium salt.

14. Compositions as claimed in claim 13 wherein the said quaternary ammonium salt comprises methacrylyloxyethyl - trimethyl-ammonium chloride.

15. Compositions as claimed in any of the preceding claims wherein the polymer contains cross-linking bridges derived from a monomer containing at least two polymerisable double bonds per molecule.

16. Compositions as claimed in claim 15 wherein the said cross-linking bridges are derived from divinyl benzene or glycol dimethacrylate monomer units.

17. Compositions as claimed in any of the preceding claims in the form of tablets, granulates or powders provided with at least one of the said protective coatings.

18. Compositions as claimed in any of claims 1 to 16 in the form of capsules having a protective shell.

19. Compositions as claimed in claim 1 substantially as herein described.

20. Pharmaceutical compositions for oral administration, substantially as herein described in any of the Examples.

21. A process for the preparation of pharmaceutical compositions for oral administration which comprises applying to discrete units of therapeutic material at least one coating of an aqueous dispersion (as hereinbefore defined) of a polymer containing 10 to 55% by weight of units at least one olefinically unsaturated monomer containing one or more carboxy groups and/or one or more monoalkyl- or dialkyl- aminoalkyl or β - morpholino- or β - piperidinoethyl carboxylate ester groups with subsequent drying to form a protective coating.

22. A process as claimed in claim 21 wherein the said dispersion has a solids content of 20 to 50% by weight.

23. A process as claimed in claim 21 where-

in the polymer is as defined in claim 2 or claim 3.

24. A process as claimed in claim 23 wherein the said dispersion contains an anionic emulsifier.

25. A process as claimed in claim 24 wherein the anionic emulsifier comprises a soap or a product derived from the sulphation and neutralisation of an ethoxylated fatty alcohol, fatty acid amide or alkyl phenol.

26. A process as claimed in claim 21 wherein the polymer is as defined in claim 4 or claim 5.

27. A process as claimed in claim 26 wherein the said dispersion contains a cationic emulsifier.

28. A process as claimed in claim 27 wherein the cationic emulsifier comprises (diisobutylphenoxyethoxyethyl) - dimethylbenzyl - ammonium chloride or stearyl - dimethyl - benzyl - ammonium chloride.

29. A process as claimed in any of claims 24, 25, 27 and 28 wherein the said dispersion further contains a non-ionic emulsifier.

30. A process as claimed in claim 29 wherein the non-ionic emulsifier comprises an ethoxylated fatty alcohol, fatty acid amide or alkyl phenol.

31. A process as claimed in any of claims 24, 25 and 27 to 30 wherein the dispersion contains at least 0.5% of emulsifier (based on the weight of the aqueous phase).

32. A process as claimed in claim 31 wherein the dispersion contains 1 to 5% of emulsifier.

33. A process as claimed in any of claims 21 to 32 wherein the coating composition is applied by spraying.

34. A process as claimed in any of claims 21 to 33 wherein the therapeutic material is provided with a protective coating having a total thickness of 10 to 50 mμ.

35. A process as claimed in any of claims 21 to 33 wherein the therapeutic material is provided with a protective coating containing a pigment or other adjuvant and having a total thickness of 20 to 200 mμ.

36. A process as claimed in any of claims 21 to 35 wherein the therapeutic material is in the form of tablets, coated tablets, capsules, micro-dragees, granulates or powders.

37. A process as claimed in any of claims 21 to 36 in which a therapeutic material is incorporated between two successive coatings of the said aqueous dispersion.

38. A process as claimed in claim 1 substantially as herein described.

39. A process for the production of pharmaceutical compositions substantially as herein described in any of the Examples.

40. Pharmaceutical compositions whenever prepared by a process as claimed in any of claims 21 to 39.

41. A process for the production of pharmaceutical capsule shells which comprises coating the surface of a mould with a composition comprising an aqueous dispersion (as hereinbefore defined) of a polymer containing 10 to 55% by weight of units from at least one olefinically unsaturated monomer containing one or more carboxy groups and/or one or more monoalkyl- or dialkyl-aminoalkyl or β-morpholino- or β-piperidino-ethyl carboxylate ester groups, the coating being subsequently dried and removed from the mould.

42. A process as claimed in claim 41 wherein coating is effected by immersing the mould in the said composition and subsequently withdrawing the coated mould from the said composition.

43. A process as claimed in claim 41 wherein coating is effected by spraying the said composition on to the surface of the mould.

44. A process as claimed in claim 41 substantially as herein described.

45. A process for the production of pharmaceutical capsule shells substantially as herein described in any of Examples 12 to 14.

46. Pharmaceutical capsule shells whenever prepared by a process as claimed in any of claims 41 to 45.

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